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Total Synthesis

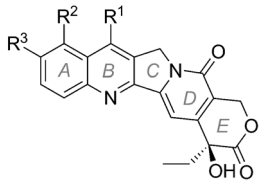
Short Protecting Group-free Syntheses of Camptothecin and 10-Hydroxycamptothecin Using Cascade Methodologies

Peng Xu, Dong-Sheng Chen, Jie Xi, and Zhu-Jun Yao*[a]

Abstract: A convergent protecting group-free total synthesis route of camptothecin and 10-hydroxycamptothecin has been developed in this work. Cascade oxidation of 3-(hydroxymethyl)furan-2(5*H*)-one and in situ intermolecular oxa Diels–Alder reaction with vinyl ether was developed and applied to construct the E-ring, and TMSCl-promoted cascade closure of the D-ring delivered the whole skeleton of the alkaloids in the total synthesis. The new short syntheses were advantageous with regard to step economy, low cost, easily available starting materials and reagents, and convenient operations.

Introduction

Camptothecin (CPT, **1a**, Figure 1) was discovered as a unique pentacyclic quinoline alkaloid from *Camptotheca acuminate* (Xi Shu) that originated in China by Wall and co-workers in 1966.[1] Due to its potent cytotoxicity and great potential in anticancer drug development, this natural product has attracted great interest of medicinal and synthetic chemists since the 1970s.[2] In clinical trials its sodium salt was initially used because of the poor water-solubility of CPT. Although the unsatisfactory biological activity and severe side effects resulted in suspension of the trials,[3] the discovery of DNA topoisomerase I (Topo I) as the cellular target of CPT renewed the research on CPT.[4] Ultimately, topotecan (**1c**)[5] and irinotecan (**1d**),[6] two CPT analogues, were launched for clinical practice, and several other analogues are currently developed into various stages of clinical trials.[7]



Camptothecin (**1a**: $R^1 = R^2 = R^3 = H$)
10-Hydroxycamptothecin (**1b**: $R^1 = R^2 = H$; $R^3 = OH$)
Topotecan (**1c**: $R^1 = H$, $R^2 = CH_2NMe_2$, $R^3 = OH$)
Irinotecan (**1d**: $R^1 = Et$, $R^2 = H$, $R^3 = OCOPipPip$)

Figure 1. Camptothecin and representative derivatives.

Since the first total synthesis of *rac*-camptothecin by Stork and Schultz in 1971,[8a] quite a number of total syntheses of CPT and its derivatives have emerged over the past few decades, in which excellent chemistries have been reported.[8–10] However, most of currently available chemical syntheses of camptothecin could not fully meet the requirements of large-scale preparation and industrial-scale production yet, and the pharmaceutical supply of raw material is now mainly dependent on extraction from medical plants. On the other hand, discovery of antitumoral camptothecin derivatives have also been achieved, mainly through traditional chemical modifications of the natural product. Therefore, development of a practical and economic route is of extreme importance for the future natural source-free production of alkaloids of the CPT family and diversification of the scope of CPT derivatives.

Our laboratory has been dedicated to developing efficient syntheses of CPT and derivatives for several years. In 2007, we reported a mild and efficient synthesis of CPT (**1a**) through simultaneous construction of the B/C rings with an intramolecular aza Diels–Alder reaction (Figure 2), which was promoted by the Hendrickson's reagent in excellent yield.[11] Though it greatly improved the chemical yield using Me_3OBF_4 to activate the amide functionality,[12] use of expensive and air-sensitive organometallic reagents in the preparation of the D/E rings[13] and production of a large amount of Ph_3PO in the key step increased the difficulty of product separation and the cost of large-scale synthesis. Another straightforward route utilizing an intramolecular oxa Diels–Alder reaction to simultaneously construct the C/D rings was also disclosed by us in 2008[14] (Figure 2). It constitutes the first route to synthesize CPT alkaloids without using air-sensitive and noble metal reagents so far. However, low concentration (< 0.05 M of the substrates)

[a] *Dr. P. Xu, D.-S. Chen, J. Xi, Prof. Dr. Z.-J. Yao*
State Key Laboratory of Coordination Chemistry
Institute of Chemistry Biology and Drug Innovation
School of Chemistry and Chemical Engineering
Nanjing University
22 Hankou Road, Nanjing, Jiangsu 210093 (China)
E-mail: yaoz@nju.edu.cn

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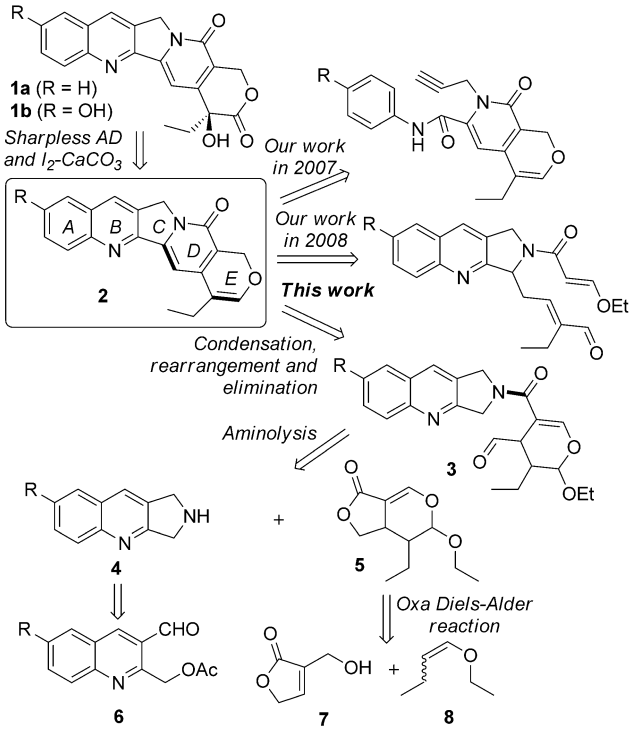


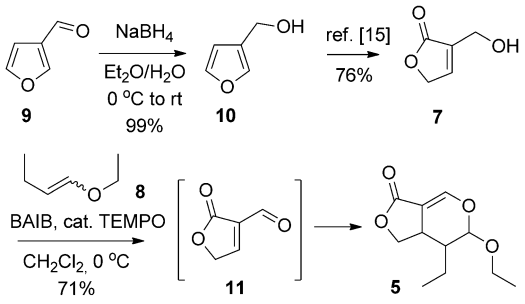
Figure 2. Retrosynthesis of camptothecin and its derivatives in this work.

and high temperature (>120 °C) in the key intramolecular oxa Diels–Alder reaction were less ideal for the large-scale synthesis. To further improve the previous syntheses, a much milder intermolecular oxa Diels–Alder approach with higher substrate concentrations was thus studied and expected to be applied to the syntheses of CPT alkaloids in our laboratory. In this article, we report our recent results on the development of a new short convergent synthesis of camptothecin (**1a**) and 10-hydroxycamptothecin (**1b**), in which three cascade reactions were accordingly designed, developed and served as the key procedures for constructing the B, D, and E rings (Figure 2), respectively.

Results and Discussion

According to the retrosynthesis shown in Figure 2, the full-ring skeleton **2**[11,14] could be accomplished from compound **3** with a newly designed sequence of condensation, rearrangement, and elimination. The late-stage intermediate, amide **3**, could be synthesized through a convergent coupling of the A/B/C-ring amine **4** with lactone **5**, which would be a commonly useful E-ring building block of many important druggable camptothecin derivatives.

Our total synthesis of CPT commenced with the preparation of the E ring precursor **5** (Scheme 1). To achieve the above purpose, a quick and efficient synthesis was attempted using the intermolecular oxa Diels–Alder approach, which was expected to overcome the problems of low substrate concentration and high reaction temperature in our previous synthesis with the intramolecular oxa Diels–Alder reaction.[14] Furthermore, such

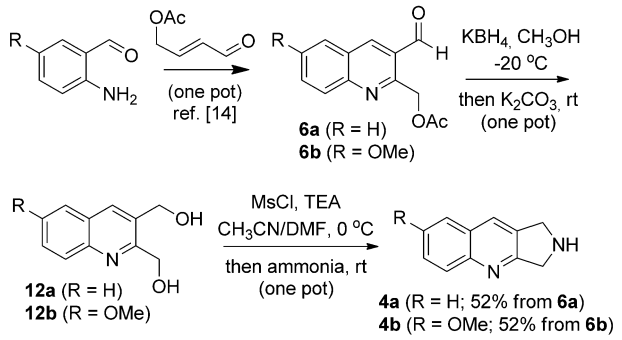


Scheme 1. Synthesis of the E-ring precursor **5** through cascade BAIB/TEMPO oxidation and oxa Diels–Alder reaction.

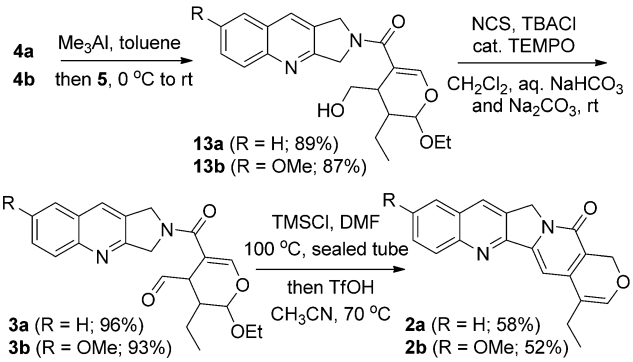
an approach would avoid the use of *t*BuLi and $Pd(OAc)_2$ in the synthesis of the E ring[7,11,12] and thus would reduce the cost of future industrial-scale synthesis. The commercially available economic material, furan-3-carbaldehyde (**9**), was firstly reduced to furan-3-ylmethanol (**10**) with $NaBH_4$ in 99% yield, which was further transformed into the corresponding lactone **7** under the known conditions.[15] Logically, actone-alcohol **7** should be oxidized to the α, β-unsaturated aldehyde **11** at first, and the resulting **11** would then be applied to the oxa Diels–Alder reaction with enol ether **8**. Unfortunately, α, β-unsaturated aldehyde **11** was found to be unstable (or exist with a short lifetime) in the reaction media. We could not observe the existence of the desired product **11** in the reactions after attempting a variety of oxidants, including PDC, PCC, DMP and MnO_2. Such a problem prompted us to consider in situ capture of the newly formed aldehyde **11** with electron-rich dienophile **8** during the oxidation process. To our delight, combinative use of 1-ethoxybut-1-ene **8**[16] in the oxidation of **10** directly afforded the expected E ring precursor, lactone **5**, as a mixture of diastereomers. After screening various oxidants, such as DMP, PCC, PDC and Parikh–Doering oxidation reagent, mild bis(acetoxy)iodobenzene (BAIB)/2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) oxidation[17] was proven to be the best conditions to prepare the lactone **5** in 71% yield in a cascade fashion.

Another crucial A/B/C-ring fragment (compounds **4a** and **4b**, for the synthesis of CPT and 10-hydroxycamptothecin, respectively) could be prepared in few steps from the corresponding quinoline derivatives **6a** and **6b**, which were easily synthesized through the cascade reaction (pyrrolidine/$PhCO_2H$ catalysed Michael addition, intramolecular aldol condensation and in situ MnO_2 oxidation) developed in our previous work[14] (Scheme 2). Reduction of the aldehydes **6** with KBH_4 in methanol followed by removal of the acetate with K_2CO_3 in one pot afforded diols **12** in high yield. Diols **12** were further converted into the tricyclic amines **4** (in 52% overall yield from **6**) through mild O-mesylation and subsequent treatment with aqueous ammonium hydroxide in the same pot.[18] In our practice, the diols **12** were pure enough and could be used directly in the next step.

With both fragments **4a/4b** and **5** in hand, our endeavor continued toward the synthesis of the whole skeletons **2** (Scheme 3). Couplings of lactone **5** with amines **4a/4b** were



Scheme 2. Synthesis of the tricyclic amines **4a** and **4b**.



Scheme 3. Coupling of fragments **4** and **5**, and synthesis of pentacycle **2**.

successfully achieved by trimethylaluminum-mediated aminolysis, affording the alcohols **13a/13b** in good yields. Mild TEMPO/NCS (N-chlorosuccinimide) oxidations[19] of alcohol **13a** and **13b** were carried out in the mixed reaction media of dichloromethane and aqueous $NaHCO_3/K_2CO_3$ solution (0.5 M of $NaHCO_3$ and 0.05 M K_2CO_3), providing aldehydes **3a** and **3b** in high yields.

Closure of the D-ring via the intramolecular condensation of the aldehyde group and the pyrrolidine α-methylene of **3a** and **3b** was found to be troublesome. Literature conditions, such as Ac_2O[8f] and NaOAc/HOAc,[18] did not work at all in these two cases. Though the reaction of **3a** with *t*BuOK/DMF[20] provided a low yield (< 10%) of the expected product, further optimizations all failed to improve the yield of the product. The disappointing results under strong or weak basic conditions led us to consider alternative conditions with economically available Lewis acids. After a number of attempts, treatment of **3a** with TMSCl/DMF[21] was found to provide compounds **14a** and **2a** simultaneously in an improved yield (20–30%, in a ratio of 2:3) (Figure 3). Based on these data, it was envisioned that the transformation might be carried out through a cascade sequence of aldehyde condensation, olefin rearrangement, and elimination of ethanol. However, the yield of **2a** remained unsatisfactory (up to 44% yield) even after further optimizations of reaction conditions, such as increasing the amount of TMSCl and reaction time, altering the reaction temperature, as well as changing the solvent. Eventually, the

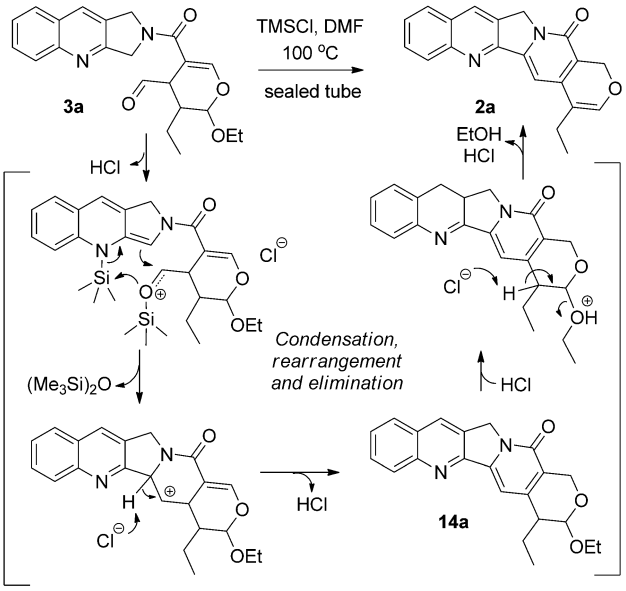
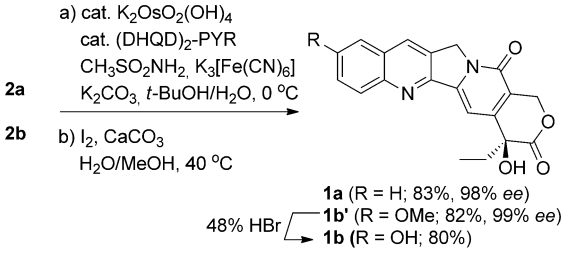


Figure 3. Proposed mechanism of the TMSCl-promoted tandem cyclization.

desired product **2a** was obtained in up to 58% overall yield by further treatment of the resulting mixture (immediately from the reaction with TMSCl/DMF) with TfOH in CH_3CN at 70 °C (Scheme 3). It is plausible that elimination of the TMS oxy group or hydroxy group from the intermediate was accelerated by the addition of TfOH. Utilizing the same approach, we also successfully prepared the other pentacyclic intermediate **2b** in 52% overall yield. Finally, the two-step oxidations (Sharpless asymmetric dihydroxylation followed by iodine-based hemi-acetal oxidation)[11,14,22,23] smoothly converted the pentacyclic intermediates **2a** and **2b** into (*S*)-camptothecin (**1a**) and (*S*)-10-methoxycamptothecin (**1b′**), respectively, with excellent yields and enantiopurities (Scheme 4). Removal of the *O*-methyl group of (*S*)-10-methoxycamptothecin (**1b′**) was carried out with 48% aqueous HBr solution, affording (*S*)-10-hydroxycamptothecin (**1b**) in 80% yield.[14]



Scheme 4. Completion of the total synthesis.

Conclusions

In summary, we have successfully accomplished a new short convergent total synthesis route for the well-known anticancer alkaloids camptothecin (**1a**, 16% overall yield from 2-aminobenzaldehye, 8 steps) and 10-hydroxycamptothecin (**1b**, 10%

overall yield from 2-amino-5-methoxybenzaldehye, 9 steps) with simple and inexpensive starting materials and reagents. Three cascade reactions and one-pot treatments were designed, developed, and successfully applied to this synthesis, including construction of the E-ring with cascade allylic alcohol oxidation and intermolecular oxa Diels–Alder reaction under mild conditions, preparation of the AB-ring system with mild cascade pyrrolidine/$PhCO_2H$-catalyzed aza Michael addition, and intramolecular aldol reaction and in situ MnO_2 oxidation, and closure of the D-ring with cascade TMSCl-promoted condensation, olefin migration, and ethanol elimination. The reproted protecting group-free total synthesis, with advantages of a short route, simple operations, and mild conditions, is believed to be helpful for the future development of industry-scale syntheses of camptothecin-family alkaloids.

Experimental Section

General. Unless stated otherwise, all solvents were purified and dried prior to use. IR spectra were recorded on a Bruker TENSOR 27 or VECTOR 22 FT-IR instrument. Reference peaks for chloroform in ^{1}H NMR and ^{13}C NMR spectra were set at 7.26 ppm and 77.16 ppm, respectively. For [D_4]MeOH, the reference peaks in ^{1}H NMR and ^{13}C NMR spectra were set at 3.31 ppm and 49.00 ppm, respectively. Flash chromatography was performed on silica gel (300–400 mesh).

Compound 5. To a stirred solution of 3-(hydroxymethyl)furan-2(5H)-one (**7**) (8.9 g, 78 mmol) and vinylether **8** (38 g, 379 mmol) in CH_2Cl_2 (460 mL) was added bis(acetoxy)iodobenzene (BAIB, 33 g, 102 mmol) and TEMPO (1.8 g, 11.5 mmol) successively at 0 °C. After being stirred at the same temperature for 24 h, the reaction mixture was quenched by the addition of saturated aqueous $Na_2S_2O_3$ solution. The aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography on silica gel (petroleum ether/ethyl acetate = 5:1) to afford **5** (11.8 g, 71%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.81–0.98 (3H, m), 1.16–1.28 (3H, m), 1.33–1.40 (1H, m), 1.50–1.56 (1H, m), 1.71–1.80 (1H, m), 2.95–3.54 (1H, m), 3.60–3.65 (1H, m), 3.80–4.08 (2H, m), 4.43–4.62 (1H, m), 4.82–5.10 (1H, m), 7.35–7.43 (1H, m) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 10.8, 11.3, 11.9, 14.7, 14.8, 14.81, 17.1, 22.6, 22.8, 31.7, 33.8, 35.5, 37.8, 41.4, 41.6, 64.4, 64.6, 65.7, 67.5, 71.4, 71.6, 99.1, 99.2, 103.7, 103.8, 104.4, 147.9, 148.1, 149.6, 169.8 ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3075, 2974, 2935, 2898, 2879, 1759, 1670, 1459, 1379, 1341, 1236, 1150, 1105, 1019, 875, 836, 753 cm^{-1}. HRMS (ESI, *m/z*) calcd. for $C_{11}H_{16}O_4$ $(M+H)^+$: 213.1122; found: 213.1135.

Compound 12a. To a stirred solution of **6a** (5.7 g, 25 mmol) in MeOH (110 mL) was added KBH_4 (1.1 g, 20 mmol) in small portions at −20 °C. When the substrate was consumed (the reaction usually completed within 10 min), K_2CO_3 (6.9 g, 50 mmol) was added. The reaction was allowed to warm to room temperature and stirred for additional 10 min. The solvent was removed under vacuum and the residue was dissolved in 55 mL of H_2O. The aqueous layer was extracted with warmed ethyl acetate. The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and evaporated to dryness to give a yellow solid **12a** (crude yield 100%),[18] which was pure enough to use in the next step without further purification. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.83 (2H, s), 4.92 (2H, s), 7.55–7.60 (1H, m), 7.72–7.77 (1H, m), 7.87 (1H, d, *J* = 9.0 Hz), 8.10 (1H, d, *J* = 6.0 Hz), 8.20 (1H, s) ppm. ESIMS (*m/z*): 190.33 $(M+H)^+$.

Compound of 12b. The same procedure for **12a** was used for preparation of **12b** (crude yield 100%). Mp: 138–140 °C. ^{1}H NMR (500 MHz, CD_3OD): δ = 3.89 (3H, s), 4.84 (2H, s), 4.86 (2H, s), 7.19 (1H, d, *J* = 2.0 Hz), 7.31 (1H, dd, J_1 = 9.5 Hz, J_2 = 2.5 Hz), 7.88(1H, d, *J* = 9.5 Hz), 8.15 (1H, s) ppm. ^{13}C NMR (125 MHz, CD_3OD): δ = 56.1, 61.8, 64.3, 106.4, 123.2, 130.2, 130.4, 134.5, 135.4, 143.1, 156.7, 159.6 ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3353, 3130, 3075, 3001, 2971, 2926, 2875, 2835, 1623, 1605, 1500, 1468, 1431, 1385, 1353, 1303, 1226, 1185, 1169, 1136, 1107, 1052, 1028, 977, 959, 917, 854, 833, 790, 759, 628 cm^{-1}. HRMS (ESI, *m/z*) calcd. for $C_{12}H_{13}NO_3$ $(M+H)^+$: 220.0969; found: 220.0995.

Compound 4a. To a stirred solution of crude **12a** (2.0 g) in DMF (33 mL) and CH_3CN (200 mL) was successively added Et_3N (5.9 mL, 42 mmol) and MsCl (2.5 mL, 32 mmol) at 0 °C under N_2 atmosphere. After being stirred for 5 min, excess concentrated NH_4OH solution (35%, 300 mL) was added. The reaction was allowed to warm to room temperature and stirred for additional 1 h. The reaction mixture was extracted with $CHCl_3$. The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography on silica gel (CH_2Cl_2/CH_3OH = 4:1) to afford **4a** (1.03 g, 52%, from **6a**) as a pale yellow solid.[18] ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.03 (1H, br s), 4.44 (2H, s), 4.49 (2H, s), 7.54 (1H, t, *J* = 7.5 Hz), 7.70 (1H, t, *J* = 7.5 Hz), 7.81 (1H, d, *J* = 8.1 Hz), 7.98 (1H, s), 8.06 (1H, d, *J* = 8.7 Hz) ppm. ESIMS (*m/z*) : 171.25 $(M+H)^+$.

Compound 4b. The same procedure for **4a** was used for the preparation of **4b**. Flash chromatography (CH_2Cl_2/MeOH = 4:1) afforded **4b** (52%, from **6b**) as a pale yellow solid. Mp: 113 °C (dec.). ^{1}H NMR (500 MHz, CD_3OD): δ = 3.92 (3H, s), 4.39 (2H, s), 4.51 (2H, s), 4.88 (1H, s), 7.27 (1H, d, *J* = 2.5 Hz), 7.36 (1H, dd, J_1 = 9.5 Hz, J_2 = 2.5 Hz), 7.85 (1H, d, J_1 = 9.5 Hz), 8.12 (1H, s) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 50.8, 52.2, 56.1, 107.1, 123.5, 130.0, 130.2, 130.8, 132.0, 144.6, 159.5, 160.3 ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3421, 3064, 3003, 2959, 2925, 2851, 1622, 1585, 1502, 1453, 1367, 1299, 1224, 1159, 1127, 1101, 1027, 826 cm^{-1}. HRMS (EI, *m/z*) calcd. for $C_{12}H_{12}N_2O$ $(M^{+\cdot})$: 200.0950; found: 200.0961.

Compound 13a. To a solution of tricyclic amine **4a** (510 mg, 3.0 mmol) in toluene (25 mL) was added Me_3Al (2.0 M in toluene, 1.8 mL, 3.6 mmol) dropwise at 0 °C under N_2 atmosphere. The reaction was then warmed to room temperature. After being stirred for 1 h, the reaction mixture was once again cooled down to 0 °C. A solution of lactone **5** (635 mg, 3.0 mmol) in toluene (3 mL) was then added dropwise. The reaction was allowed to warm to room temperature and stirred for 16 h. The reaction was quenched successively with 0.5 M HCl and H_2O (30 mL) at 0 °C. The aqueous layer was extracted with ethyl acetate. The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography on silica gel (CH_2Cl_2/CH_3OH = 25:1) to afford **13a** (1.02 g, 89%) as a pale yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.91–0.98 (3H, m), 1.21–1.25 (3H, m), 1.33–1.63 (2H, m), 1.85–1.89 (1H, m), 2.52–2.90 (1H, m), 3.59–3.63 (2H, m), 3.72–3.76 (1H, m), 3.85–4.35 (2H, m), 4.95–5.03 (5H, m), 6.74–6.90(1H, m), 7.44–7.49 (1H, m), 7.60–7.71 (2H, m), 7.82 (1H, s), 7.93–7.96 (1H, m) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.60, 11.62, 15.22, 15.26, 19.6, 20.2, 35.6, 37.7, 38.8, 41.1, 61.7, 62.8, 64.7, 65.1, 98.8, 101.3, 111.3, 111.7, 126.6, 127.4, 127.8, 128.3, 128.7, 129.6, 129.8, 145.2, 146.7, 148.0, 159.1, 170.3, 170.6 ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3382, 3061, 2965, 2931, 2874, 1641, 1602, 1502, 1437, 1409, 1379, 1329, 1225, 1203, 1167, 1131, 1109, 1077, 1041, 982, 906, 781, 749 cm^{-1}. HRMS (ESI, *m/z*) calcd. for $C_{22}H_{26}N_2O_4$ $(M+H)^+$: 383.1965; found: 383.1973.

Compound 13b. The same procedure for **13a** was applied for the preparation of **13b**. Flash chromatography (CH_2Cl_2/MeOH = 25:1)

afforded **13b** (87%) as a pale yellow solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.95–1.12 (3H, m), 1.23–1.29 (3H, m), 1.34–1.67 (2H, m), 1.84–1.89 (1H, m), 2.51–2.92 (1H, m), 3.59–4.16 (8H, m), 4.92–5.11 (5H, m), 6.75–6.93 (1H, m), 7.01–7.03 (1H, m), 7.30–7.34 (1H, m), 7.83–7.90 (2H, m) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 11.7, 12.0, 15.2, 15.27, 15.34, 19.7, 24.8, 29.8, 35.8, 37.7, 37.8, 38.9, 41.3, 41.7, 55.58, 55.63, 62.1, 64.6, 64.8, 65.1, 66.2, 98.8, 99.0, 101.3, 105.58, 105.61, 111.5, 111.7, 122.2, 122.3, 128.6, 128.68, 128.74, 128.9, 130.1, 130.2, 144.0, 144.2, 144.3, 146.8, 156.5, 156.8, 157.87, 157.92, 170.3, 170.7 ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3444, 3063, 2964, 2926, 2875, 1651, 1622, 1505, 1434, 1404, 1369, 1314, 1292, 1261, 1226, 1165, 1137, 1093, 1027, 900, 828, 804, 768, 741 cm^{-1}. HRMS (ESI, *m/z*) calcd. for $C_{23}H_{28}N_2O_5$ $(M+H)^+$: 413.2071; found: 413.2079.

Compound 3a. To a vigorously stirred solution of alcohol **13a** (124 mg, 0.3 mmol) in CH_2Cl_2 (3.3 mL) and buffer solution (3.3 mL, 0.5 M $NaHCO_3$ and 0.05 M K_2CO_3) was added TBACl (8 mg, 0.03 mmol), NCS (88 mg, 0.7 mmol), and TEMPO (5.2 mg, 0.03 mmol) successively at room temperature. After being stirred for 2 h, the reaction mixture was quenched by the addition of saturated aqueous $Na_2S_2O_3$ solution. The aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography on silica gel (CH_2Cl_2/MeOH = 25:1) to afford **3a** (119 mg, 96%) as a pale yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.95–1.08 (3H, m), 1.14–1.27 (3H, m), 1.42–1.47 (1H, m), 1.60–1.68 (1H, m), 2.03–2.41 (1H, m), 3.28–3.48 (1H, m), 3.58–3.66 (1H, m), 3.76–3.93 (1H, m), 4.75–5.48 (5H, m), 6.93–7.10(1H, m), 7.51–7.56 (1H, m), 7.67–7.72 (1H, m), 7.79–7.82 (1H, m), 8.02–8.05 (2H, m), 9.53–9.66 (1H, m) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.4, 11.7, 11.8, 15.0, 15.1, 20.3, 21.0, 22.5, 37.5, 38.2, 45.2, 46.6, 48.3, 63.9, 65.0, 77.4, 97.9, 98.4, 107.6, 108.1, 126.4, 126.5, 127.4, 127.8, 128.2, 128.5, 128.7, 129.46, 129.5, 129.8, 144.6, 147.9, 148.0, 159.1, 159.4, 168.35, 168.4, 169.3, 200.3, 200.5, 200.9 ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3057, 2966, 2924, 2876, 2827, 2731, 1733, 1717, 1701, 1685, 1647, 1636, 1624, 1577, 1560, 1542, 1508, 1473, 1458, 1437, 1418, 1397, 1375, 1363, 1339, 1313, 1251, 1163, 1088, 909, 734 cm^{-1}. HRMS (ESI, *m/z*) calcd. for $C_{22}H_{24}N_2O_4$ $(M+H)^+$: 381.1809; found: 381.1814.

Compound 3b. The same procedure for **3a** was applied to the preparation of **3b**. Flash chromatography (CH_2Cl_2/MeOH = 25:1) afforded **3b** (93%) as a pale yellow solid. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.96–1.19 (6H, m), 1.34–1.44 (1H, m), 1.47–1.57 (1H, m), 2.19–2.44 (1H, m), 3.27–3.48 (1H, m), 3.52–3.67 (1H, m), 3.73–3.82 (1H, m), 3.92–3.93 (3H, m), 5.00–5.17 (5H, m), 6.93–7.10(2H, m), 7.33–7.36 (1H, m), 7.92–7.94 (2H, m), 9.53–9.77 (1H, m) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz): δ = 11.6, 11.8, 12.0, 14.2, 15.17, 15.2, 21.2, 22.7, 22.8, 25.0, 29.4, 29.5, 29.6, 29.7, 29.77, 29.81, 34.0, 37.7, 38.5, 45.5, 46.4, 46.8, 48.5, 55.7, 64.1, 65.2, 98.2, 98.5, 105.7, 108.3, 122.3, 122.4, 128.7, 128.9, 129.0, 130.2, 131.5, 144.3, 144.7, 156.9, 157.9, 158.0, 169.5, 201.1 ppm. IR (KBr): $\tilde{\nu}_{max}$ = 3068, 2964, 2928, 2874, 2854, 1722, 1650, 1623, 1505, 1431, 1407, 1371, 1316, 1293, 1260, 1228, 1160, 1138, 1092, 1028, 903, 830, 800, 744 cm^{-1}. HRMS (ESI, *m/z*) calcd. for $C_{23}H_{26}N_2O_5$ $(M+H)^+$: 411.1915; found: 411.1918.

Synthesis of 2a. To a sealed tube containing **3a** (150 mg, 0.39 mmol) in DMF (23 mL) was added TMSCl (126 μL, 0.98 mmol) under nitrogen atmosphere. The reaction was heated at 100 °C for 12 h. After being cooled down to room temperature, the reaction solvent was removed under vacuum. The residue was dissolved in 30 mL of CH_2Cl_2 and then successively washed with saturated aqueous $NaHCO_3$ solution (20 mL x 2) and brine (20 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated. The resulting residue was re-dissolved in 25 mL of CH_3CN under nitrogen atmosphere and TfOH (34 μL, 0.39 mmol) was added. The reaction was then heated to 70 °C and stirred for 1.5 h. After being cooled down to room temperature, the solvent was removed under vacuum. The residue was dissolved in 30 mL of CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$ solution (20 mL x 2) and brine (20 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated. The residue was purified by flash chromatography on silica gel (CH_2Cl_2/CH_3OH = 100:1) to afford **2a** (73 mg, 58%)[11,14] as a pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.22 (3H, t, J = 7.2 Hz), 2.47 (2H, q, J = 7.2 Hz), 5.19 (2H, s), 5.28 (2H, s), 6.67 (1H, s), 7.23 (1H, s), 7.65 (1H, t, J = 8.0 Hz), 7.82 (1H, t, J = 8.4 Hz), 7.93 (1H, d, J = 7.6 Hz), 8.23 (1H, d, J = 8.8 Hz), 8.37 (1H, s) ppm. ESIMS (*m/z*): 317 $(M+H)^+$.

Synthesis of 2b. The same procedure for **2a** was used for the preparation of **2b**.[14] Flash chromatography (CH_2Cl_2/MeOH = 100:1) afforded **2b** (52%) as a pale yellow solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.20 (3H, t, J = 7.5 Hz), 2.43 (2H, q, J = 7.5 Hz), 3.96 (3H, s), 5.15 (2H, s), 5.16 (2H, s), 6.64 (1H, s), 7.08–7.10 (2H, m), 7.42 (1H, dd, J = 9.3 Hz, J = 2.7 Hz), 8.06 (1H, d, J = 9.3 Hz), 8.14 (1H, s) ppm. ESIMS (*m/z*): 347 $(M+H)^+$.

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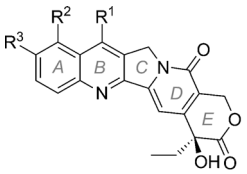
FULL PAPER

A few steps ahead: A step-economic protecting group-free total synthesis route of camptothecin (**1a**) and 10-hydroxycamptothecin (**1b**) has been accomplished in 8–9 longest linear steps from inexpensive and easily available starting materials. Three cascade reactions were accordingly designed, developed, and successfully applied to the construction of A/B-, E-, and D-rings, respectively.



Camptothecin (**1a**: $R^1 = R^2 = R^3 = H$)
10-Hydroxycamptothecin (**1b**: $R^1 = R^2 = H$; $R^3 = OH$)
Topotecan (**1c**: $R^1 = H$, $R^2 = CH_2NMe_2$, $R^3 = OH$)
Irinotecan (**1d**: $R^1 = Et$, $R^2 = H$, $R^3 = OCOPipPip$)

Total Synthesis

*Peng Xu, Dong-Sheng Chen, Jie Xi, Zhu-Jun Yao**

■■ – ■■

Short Protecting Group-free Syntheses of Camptothecin and 10-Hydroxycamptothecin Using Cascade Methodologies